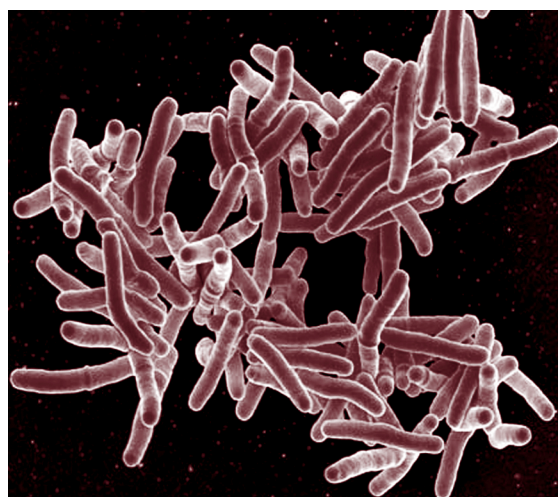


TUBERCULOSIS

NIAID plays a lead role in the NIH tuberculosis (TB) research program. In response to ongoing concern about increasing worldwide case rates and the development of multidrug-resistant strains of *Mycobacterium tuberculosis* (*M.tb*), the pathogen that causes TB, NIAID has increased its TB research portfolio steadily over the past decade. The World Health Organization (WHO) estimates that there are approximately 8 million new TB cases annually, with 2 million deaths. This toll makes TB the leading cause of death from a single infectious pathogen worldwide, killing more people than AIDS and malaria combined. Approximately one-third of the world's population is infected with *M.tb*, and 1 in 10 of these individuals likely will develop active TB disease in their lifetimes. If current trends continue, an estimated 1 billion people will be newly infected by the year 2020; approximately 200 million people will develop active TB, and 35 million will die.⁵¹

NIAID supports a broad TB research program, primarily through its extramural Division of Microbiology and Infectious Diseases (DMID), with particular emphasis on the following areas:

- Basic biology and pathogenesis of *M.tb*, host-pathogen interaction, and host response to TB in animal models and humans;
- Research into the various stages of TB, including persistent, asymptomatic infection with *M.tb* (latency), reactivation, and progression to TB;
- Development and testing of vaccines, chemotherapeutics, and diagnostics;
- Development of improved tools for epidemiologic studies; and
- Mycobacterial genomics and postgenomic analyses.



Mycobacterium tuberculosis, the organism that causes tuberculosis (Colorized electron micrograph magnification)

Recent funding increases have allowed the Institute to support a number of initiatives and to markedly expand the community of TB researchers. Higher levels of funding enabled NIAID to establish the Tuberculosis Research Unit (TBRU) at Case Western Reserve University in 1994 (www.tbresearchunit.org). TBRU continues to make progress in developing surrogate markers of disease and human protective immunity and in conducting clinical trials of potential new TB therapeutic, preventive, and diagnostic strategies. Furthermore, well-characterized clinical samples will be available for distribution to TBRU investigators and their collaborators through a newly established repository. Activities of the TBRU are coordinated with other major organizations involved in TB research, including the Centers for Disease Control and Prevention, U.S. Agency for International Development, Food and Drug Administration, WHO, Global Alliance for TB Drug Development, and International Union Against Tuberculosis and Lung Disease, and with interested industrial partners.

NIAID's extramural TB research program currently supports more than 231 grants for basic, applied, and clinical TB research. Among the projects supported by NIAID is an award to The Institute for Genomic Research in Rockville, Maryland, to support sequencing and annotation of *Mycobacterium smegmatis* (strain MC2 155), an important model system used in TB research. *M. smegmatis* microarrays also will be produced under this grant and are expected to be distributed through the Pathogen Functional Genomics Resource Center in fiscal year 2004. (For access to genome data, see www.tigr.org/tdb/mdb/mdbinprogress.html.)

The development of improved TB vaccines, which are crucial to the long-term control of TB worldwide, is a high priority. NIAID's *Blueprint for TB Vaccine Development*, presented at the 1998 International Symposium for Tuberculosis Vaccine Development and Evaluation, outlines the specific steps needed to develop improved TB vaccines (www.niaid.nih.gov/publications/blueprint). A Department of Health and Human Services-wide task force, which includes representation from NIAID, will oversee implementation of the blueprint report. NIAID's Vaccine and Treatment Evaluation Unit in St. Louis will conduct a phase I safety and immunogenicity trial of a recombinant version of the Bacillus Calmette-Guerin vaccine, in partnership with Aeras Global TB Vaccine Foundation. This candidate vaccine was originally developed with NIAID grant support. Enrollment is expected to begin in early spring 2004.

Through the Tuberculosis Research Materials and Vaccine Testing contract with Colorado State University, NIAID provides TB research reagents to qualified investigators throughout the world, enabling them to work with

consistent, high-quality reagents. Screening potential TB vaccine candidates in appropriate animal models also is conducted through this contract. During 2003, 121 individual vaccine or adjuvant candidates were tested under this contract, with 15 vaccine testing experiments completed, 16 experiments in process, and 7 under development.

Under a contract with NIAID, Southern Research Institute in Birmingham, Alabama, maintains an NIAID-supported Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) to acquire drug candidates for screening against virulent *M.tb*, maintain a computerized chemical database of candidate structures, coordinate and distribute compounds for evaluation *in vitro* and in animal models, and report data to compound suppliers. TAACF has contacted more than 3,500 chemists throughout the world seeking candidate anti-TB compounds. TAACF has received more than 60,000 compounds from academic and private-sector investigators, principally in the United States and Europe, with growing involvement of scientists from Africa, Asia, Australia, South America, and other regions (www.taacf.org).

Contracts issued by DMID and the Division of Acquired Immunodeficiency Syndrome (DAIDS) are used to support and promote research in TB covering aspects from basic through translational to applied research. Under contract, NIAID (1) offers *M.tb*-derived research reagents and animal model screening services for candidate TB vaccines (www.cvmb.colostate.edu/microbiology/tb/top.htm); (2) offers candidate compound identification and acquisition services and *in vitro* and animal model screening services to evaluate drug candidates (www.taacf.org); (3) provides funding for the development of improved TB

vaccines using already existing technology platforms; (4) supports TBRU to conduct multidisciplinary laboratory and clinical studies to answer critical questions in human TB; to provide knowledge, tools, and technologies to improve human clinical trials in TB; and to provide the capability to conduct clinical studies for the evaluation of new or improved vaccines, therapeutics, and diagnostics (www.tbresearchunit.org); and (5) assists with technology transfer for potential commercialization of new drug discoveries for TB.

DAIDS recently awarded a high-throughput, robotics screening contract to discover new antimicrobials. This facility provides the capability of testing large chemical libraries of compounds for activity against specific biochemical drug targets and against growing microorganisms.

NIAID has established a chemical database to serve as a reference for TB drug-screening results and to stimulate the design and synthesis of new candidate drugs. A clinical trials network is evaluating existing drugs approved for other clinical indications, and the National Cooperative Drug Discovery Groups for Tuberculosis (NCDDG-TB) program is searching for new drug targets and candidate compounds against *M.tb*. NIAID also participates in a newly formed public-private partnership—the Global Alliance for Tuberculosis Drug Development—together with WHO, the Rockefeller Foundation, and other international organizations dedicated to encouraging new therapeutic advances in the absence of industrial sponsorship. Increased funding through Small Business Innovation Research grants has promoted development and evaluation of new diagnostic tests for *M.tb*.

DAIDS is supporting clinical trials of new treatment and prevention strategies for tuberculosis in the setting of HIV/AIDS. These investigations are being conducted in countries with a high burden of disease associated with both TB and HIV. The interactions of these two infections are associated with high mortality, particularly in African nations. The Comprehensive International Program of Research on AIDS (CIPRA) supports research studies designed to address important public health research questions in high-burden countries.

The Division of Allergy, Immunology, and Transplantation (DAIT) supports a number of individual research projects concerned with basic mechanisms of immunity to *M.tb*. DAIT's research goals and objectives on *M.tb* are as follows:

- Understand how the immune system recognizes and responds to bacteria such as *M.tb*, hidden within host cells, and support research on antigen presentation and stress molecule induction as they relate to activation of cell-mediated immunity to intracellular pathogens;
- Promote vaccine-relevant research to identify dominant mycobacterial antigens and novel adjuvants that induce protective cellular immune responses;
- Promote research on the development of immunologic reagents for early diagnosis and monitoring of disease; and
- Support research on the identification of immune system genes that activate in response to mycobacterial infection, especially genes that encode soluble proteins that might be relevant to the development of TB vaccines or therapies.

Research topics include T-lymphocyte recognition of mycobacterial lipid antigens, the role of various cell populations in combating *M.tb* infection, and the function of biological oxidants in protective immune processes.

DAIT supports several projects that assist research on TB as well as other infectious diseases such as hepatitis C, malaria, and HIV. Under the Application of Data on Human Leukocyte Antigen (HLA) to the Improvement of Vaccines program, DAIT supports the HLA Ligand/Motif Online Database, a Web-based, searchable database of human major histocompatibility complex (MHC) molecules and peptide ligands. The database specifies amino acid sequences of peptides derived from viral, bacterial, parasite, and human proteins in association with human class I or class II MHC molecules. This resource enables users to search for specific human MHC/peptide combinations or to determine ligand amino acid motifs that will facilitate their research. Support is provided under an NIAID contract to the University of Oklahoma. The Web address is www.hlaligand.ouhsc.edu.

The NIAID Tetramer Facility produces peptide-MHC reagents for T cell detection. Reagents this facility supplies are relevant to many vaccine topics, including intracellular bacterial, viral, and parasite infections, autoimmune diseases, and basic immunobiology. More information about this facility can be found at www.niaid.nih.gov/repos/tetramer/index.html. The National Cancer Institute also provides funding for the Tetramer Facility.

The Division of Intramural Research (DIR) has a substantial intramural program that integrates genomics and combinatorial

chemistry to speed development of new antibiotics for the control of tuberculosis. After contributing to the determination of the genomic sequence of *M.tb*, DIR investigators are now focusing on unraveling the functions of its various genes. This knowledge is critical to new drug and vaccine development and to understanding the molecular mechanisms involved in the emergence of drug resistance. For example, TB researchers have long wondered why *M.tb* has two copies of the gene that codes for an enzyme that copies DNA strands during replication. DIR scientists and South African colleagues discovered that the extra gene encodes a unique error-prone DNA repair enzyme called DnaE2, whose mistakes allow rapid emergence of resistance to antitubercular drugs. This finding was surprising because this family of enzymes normally makes perfect DNA strands during replication and previously had not been implicated in DNA repair. This new insight into *M.tb* drug resistance suggests that therapies targeted at DnaE2 might block the development of drug resistance in people taking antibiotics to treat TB.

DIR scientists also are working on a number of different approaches to improve current TB drug therapies, such as isoniazid and ethambutol, two drugs that form the backbone of modern short-course TB therapy. For example, DIR researchers are using high-throughput methods to synthesize new compounds whose chemical structures are very similar to known TB drugs. In collaboration with Sequella Inc., DIR researchers launched a project to improve the activity of ethambutol. Using solid-phase combinatorial chemistry, the researchers created and screened a library of more than 60,000 ethambutol analog compounds. Several

of these were far more active against *M.tb* than the parent compound *in vitro* and have shown promising results in animal models.

DIR scientists also are collaborating with colleagues from GlaxoSmithKline and St. Jude's Children's Hospital to develop an improved antitubercular drug based on thiolactomycin, a compound isolated from a soil bacterium. DIR collaborators at St. Jude's used X-ray crystallography to determine the

structure of thiolactomycin bound to its enzyme target. Using this structure as a guide, scientists are now synthesizing and testing derivatives of thiolactomycin that might be more active than thiolactomycin itself against tuberculosis. This partnership is a model for the development of drugs against diseases that lack the financial impact necessary to attract independent attention from the global pharmaceutical industry. DIR scientists also

Focus on

MULTIDRUG-RESISTANT TB

Treatment of TB requires patients to take up to four different drugs for between 6 and 9 months. Many patients do not complete the full course of therapy, resulting in the development of multidrug-resistant TB (MDR-TB). The incidence of MDR-TB has increased dramatically in the past decade, and drug-resistant TB strains are now present on five continents. Treatment of MDR-TB, which is as contagious as drug-susceptible TB, requires proper diagnosis and longer, more expensive therapies that are not always available in countries where they are needed most. As a result, individuals with MDR-TB often do not receive adequate treatment, remain infectious longer, and are able to spread MDR-TB to other persons.

NIAID's extramural program supports investigator-initiated research grants on all aspects of TB science, as well as the development of vaccines, drugs, and diagnostics needed to combat drug-sensitive and drug-resistant TB. MDR-TB is included in NIAID's strategic plan for biodefense pathogens under Category C—emerging and re-emerging infections. Under this initiative, investigators are encouraged to translate basic research findings rapidly into viable candidates for products that will have an impact on the spread of this deadly disease. To complement and enhance academic and private-sector efforts, NIAID also offers contract services and resources to the research community that provide important research materials; vaccine testing services in animals; drug testing services both in cell culture and in animal models of infection and disease; assistance in conducting preclinical studies with novel drug, vaccine, and diagnostic candidates; and a clinical trials infrastructure to evaluate new products in humans. As a result of these efforts, several drugs now are being evaluated for their potential to improve the current TB drug regimen and to allow better treatment of MDR-TB. Furthermore, since vaccines will present the ultimate "weapon" against drug-sensitive TB and MDR-TB, many novel vaccine candidates are developed with NIAID funds and technical assistance; two are expected to enter phase I clinical trials early in 2004. These intervention strategies are complemented by studies to develop diagnostics that will allow rapid identification of drug resistance and initiation of proper treatment.

have partnerships with colleagues from South Korea, Cambodia, and Nigeria to collaborate in studies of multidrug resistance and TB-HIV co-infection (see Global Health, page 99).

NIAID support for TB research has led to significant advances in our understanding of

the basic biology, microbiology, and immunology of TB, which will result in the development of new diagnostic tools, vaccine candidates, and therapeutic strategies to prevent and ultimately cure this devastating disease.